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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/001,267	10/31/2001	Lakshmi Rambhatla	093/004P	1874

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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 12/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/001,267	RAMBHATLA ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 23 September 2004.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 13-40 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 13-40 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's Amendment, filed 9/23//2004, has been entered. Claims 13, 27 and 28 have been amended. Claims 13-40 are pending and under current examination.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

The prior rejection of claims 13-40 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4, 6, 7, 9-13 17-19 of copending Application No. 10/087,142 is maintained for reasons of record. Applicants acknowledge the rejection and state that upon indication of patentable subject matter, Applicants undertake to file a terminal disclaimer or to take other appropriate action to obviate double patenting. (See prior Response, filed 6/9/04, p. 7).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 13-40 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. 6,458,589 B1 [published October 1, 2002].

Applicants argue that the analysis for obviousness-type double patenting is whether the invention defined in a *claim* of the present application is an obvious variation of the invention defined in a claim of the cited patent, and therefore, it is only the claims of the patent and the application which are to be compared, absent of what is taught by the specification. Applicants argue that the claims of the '589 patent cover a product, namely a set of cell populations, one of which has certain characteristics of hepatocytes. Applicants argue that nowhere in the claims of the '589 patent suggest that the heptocyte lineage cells can be generated using a histone deacetylase inhibitor.

This is not found to be persuasive because the claims of the '589 Patent disclose the exact same cell types as the instant claims. Furthermore, the methods in the instant claims start and result in the '589 cells. Thus, the methods of the instant application make obvious the cell populations of the '589 patent.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for producing hepatocytes from primate pluripotent stem (pPS) cells, comprising a) obtaining a culture of pPS cells; b) initiating differentiation of the pPS cells of the pPS cells simultaneously or subsequently, c) culturing the cells of step (b) in a medium containing 5 nM sodium butyrate, does not reasonably provide enablement for the breadth of the claims for methods for producing hepatocytes from primate pluripotent stem (pPS) cells, comprising a) obtaining a culture of pPS cells; b) initiating differentiation of the pPS cells of the pPS cells simultaneously or subsequently, c) culturing the cells of step (b) in a medium containing a histone deacetylase inhibitor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims as amended recite methods for producing hepatocytes from primate pluripotent stem (pPS) cells, comprising a) obtaining a culture of pPS cells; b) initiating differentiation of the pPS cells of the pPS cells simultaneously or subsequently, c) culturing the cells of step (b) in a medium containing a histone deacetylase inhibitor.

Applicants argue that the Lee article, which is cited in the prior Office action, helps underline the inventiveness of the claimed methods. In particular, that the article implies that histone deacetylase inhibitors would have the effect of inhibiting differentiation of ES cells, and thus, Lee teaches against the idea of using histone deacetylase inhibitors to make differentiated cell populations. Applicants point to the instant invention, which teaches that histone deacetylase inhibitors unexpectedly direct undifferentiated hES cells into a pathway that generates a highly homogenous population of hepatocyte lineage cells. Applicants argue that the specification provides support for initiating differentiation before culturing the cells with histone deacetylase inhibitor (see Examples 1 and 9), and that the specification provides support for the contacting of the hES cells with the histone deacetylase inhibitor in the initial step (Example 5). Applicants state that the hES cells are cultured in a medium containing sodium butyrate, but Applicants do not know whether the cells differentiate because of the alterations to the medium, the inhibitor, or both. Applicants argue that thus, it is unnecessary to provide evidence as to which is correct, but that the example confirms that differentiation can be initiated simultaneously to culturing with histone deacetylase inhibitor. See p. 2 of the Response.

Applicant's arguments are found to be persuasive with regard to the amendments to the claims reciting that the hES cells can be simultaneously or subsequently cultured in a medium (step c of claim 13, for example). However, the

claims are found to be enabled with regard to using 5 mM of sodium butyrate for the following reasons. The state of the art, as evidenced by Lee *et al.* (cited in the prior Office action) is that histone deacteylase is required for ES cell differentiation, but that at a concentration of 5mM, there was a more modest effect on ES cell differentiation (see p. 34, 2nd column and Figure 3 b,c). Furthermore, Lee teaches that upon withdrawal of TSA, the ES cells were able to differentiate into embryoid bodies. See p. 37, 1st column, 1st ¶. The instant specification provides support for directly differentiating hES cells to hepatocyte-like cells using 5 mM of sodium butyrate but fails to support the breadth of the claims, which is directed to using any concentration of any histone deacetylase inhibitor. Clearly, as evidenced by Lee, in lower concentrations of TSA, the ES cells were able to differentiate, but there was no observation of these cells becoming a homogenous population of cells. Thus, it would have required undue experimentation for one of skill in the art to use any histone deacetylase inhibitor, for the breadth claimed, at any concentration, to produce a homogenous population of hepatocyte-like cells, as instantly claimed.

Claim Rejections - 35 USC § 112

The prior rejection of claim 13 is withdrawn in view of Applicants' amendment to the claim which now specifically recites which cells are cultured in part (c) of the claim.

Claim Rejections - 35 USC § 102

The prior rejection of claims 27 and 31-33 is withdrawn in view of Applicants' amendment to the claims and arguments, which require the user obtain a population of cells having characteristics of hepatocytes from pPS cells, which is not taught by Kaneko *et al.* See p. 10, 3rd ¶ of the Response.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the Examiner be unavailable, inquiries should be directed to Amy Nelson, Acting SPE of Art Unit 1632, at (571) 272-0804. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

tnt
Thaian N. Ton
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AU1632